CONVALESCENT PLASMA TRIAL

Team

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Give Antibodies, Stop COVID

We seek support for immune antibody therapy, to develop and deploy an immediate response in the hopes of ***decreasing illness and death*** caused by COVID-19 in the ***first pandemic wave of 2020***. At the same time, if properly deployed, this project will add to our understanding of the natural antibody response to SARS-CoV-2 virus infection, guiding the use of future, improved antibody therapies, and assisting in the development of COVID vaccines. Support at this critical juncture will allow clinical and basic researchers at UNC to marshal considerable resources and expertise, with the potential to build towards the deployment of directed antibody therapy more broadly across North Carolina.

The pandemic of the novel coronavirus SARS-CoV-2, causative agent of COVID-19 disease, is upon North Carolina as it moves across the globe. Currently, only supportive medical care is known to improve outcomes of people with COVID. Feverish efforts of the biomedical community have begun to develop a protective vaccine, but in the best case an effective one will not be available for months. Currently only one intravenous antiviral agent (Remdesivir) appears likely to be active against the virus, but it is not clear it is helpful for those most critically ill, and is currently in limited supply.

The future course of COVID-19 is unclear. It is not known when new infections will peak, and when they will recede, if a 2nd wave of new infections will re-emerge, and if COVID will return periodically. There are now a few medicines licensed for other uses that are hoped to have clinical activity, but the expert medical community is largely skeptical of their value. It is unlikely that truly curative, breakthrough medicines or vaccines will become widely available in the next year, if then. What is needed now is an effective intervention that can be immediately deployed to decrease deaths due to COVID-19, and to buy time for novel therapies and vaccines to emerge.

Convalescent COVID-19 Plasma (CCP) therapy

COVID-19 convalescent plasma (CCP) represents the only current therapeutic option against SARS-CoV-2 that has the potential to augment virus-specific immune responses and is also scalable to deploy rapidly. Plasma from COVID-19-recovered patients is thought to contain antibodies that are directed against, and could neutralize, SARS-CoV-2. This concept of passive antibody therapy is established in clinical practice through the use of intravenous immune globulin, a concentrated antibody preparation used to augment immunity against some viral and bacterial infections. Historically, plasma from recovered patients has been used to treat other viral respiratory infection outbreaks, from the time of the 1918 Influenza pandemic to the first SARS outbreak (SARS-CoV-1) in this century.

Experience from SARS-CoV-1 shows that such convalescent plasma (CP) contains neutralizing antibodies to the relevant virus. During the 2009 H1N1 influenza outbreak, there was an 80% reduction in risk of death in severely ill patients who received plasma versus controls who declined it (p=0.011). Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in Ebola survival for those treated with convalescent whole blood relative to those who received standard treatment. A systematic review of CP use in severe acute respiratory infections identified 32 studies between 1919 and 2011 that collectively suggested a similar reduction in risk of death with this approach (OR: 0.25, 95% CI: 0.14-0.45).

Two reports of 15 CCP-treated patients in China have been published. Both of these studies reported signs of clinical improvement days after receiving CCP. There were no reports of harm. In another pilot study in Wuhan, China CCP was used to treat patients diagnosed with severe COVID. There were no serious adverse reactions recorded with CCP. There were fewer deaths in the treatment group ($p < 0.001$). These reports and others suggest convalescent plasma may hold promise for ameliorating the severity of COVID-19 and deserves immediate investigation for this indication.

How much anti-SARS-CoV-2 neutralizing antibody is needed

The therapeutic benefit of CCP is thought to be due to the presence of high concentrations of antibodies that neutralize the virus. When used for therapy, the optimal dose of neutralizing antibody in plasma has not been well defined. Studies suggests that the quality and/or quantity of neutralizing antibodies varies between individuals. Further, it is possible that too much antibody may be detrimental. A theoretical risk, not yet seen in studies administering CCP, is the phenomenon of antibody-dependent enhancement of infection, which occurs when antibodies against a viral pathogen can paradoxically worsen the viral syndrome. The FDA has authorized the use of CCP on a compassionate use basis with a recommended minimum neutralizing antibody titer of at least 1:160. However, only some antibodies against any virus can *neutralize* the virus and render it non-infectious. While there are now many assays under study to measure total antibody levels against COVID-19, tests to measure *neutralizing antibody activity* are more difficult, and less widely available.

World-class investigators at UNC (*Baric and DeSilva*) have been developing assays to measure a) *total antibody* levels to different components of SARS-CoV-2, most importantly the *spike* protein which is involved in cell entry, and b) levels of *neutralizing antibodies* which can block viral infection. At UNC we have begun to recruit individuals who have recovered from COVID-19, for CCP donation. These donor units are being tested in the Baric and DeSilva laboratories, to characterize the total level of SARS-CoV-2 antibody, the level of Spike antibody, and the level of neutralizing antibody.

We plan to compare the outcomes of hospitalized COVID-19 patients treated CCP of typical neutralization antibody titer (1:160 to 1:640) to those treated with high-titer CCP (>1:640). Already, with pilot funding and donated effort we have obtained nearly 20 CCP donations, and treated nearly a dozen patients. Expansion of this program will allow us to provide a potential therapy and answer important questions. Most critically we might learn if:

1) High-titer CCP improves outcomes, or if CCP of any titer improves outcomes
2) If the neutralization titer (a difficult assay) is predicted by the level of Spike antibody (a simple assay suitable for broad clinical laboratory use).

If successful, this program would validate and guide the best use of antibody therapy for COVID-19, and might demonstrate that a simple assay that could be widely adopted in many clinical laboratories (level of Spike antibody), could be used to select CCP donations best suited for therapeutic use.

IMPACT TO THE STATE (300 word limit)

- *Description of the problem or challenge being addressed and how the problem impacts those in the state of North Carolina*

The pandemic of COVID-19 disease, is upon North Carolina. SARS-CoV2 has caused more than 20,000 infections in NC, over 450 hospitalizations at UNC Health, and 152 at UNC Hospital. Currently, only one antiviral agent (Remdesivir) appears to have some clinical benefit, but benefit is not complete and drug supply is too limited to meet the demand.

COVID-19 convalescent plasma (CCP) is the most rapidly scalable, deployable potential therapeutic for SARS-CoV-2. The benefit of CCP is thought to be due to the presence of high concentrations of antibodies that neutralize the virus. Preliminary reports suggest that CCP is safe, and two publications of CCP-treated patients reported clinical improvement. Despite feverish efforts among commercial blood donation centers to collect CCP, the demand continues to exceed the supply. Consequently, eligible patients may wait several days and clinically worsen before receiving CCP infusion.

- *Describe how the proposed research will provide impactful solutions to the described problem to help the state of North Carolina*

The FDA recommends a minimum neutralizing antibody (nAb) titer in CCP of at least 1:160. However, CCP is typically administered without a titer, and it is not known if more antibody is better, or if too much antibody can be harmful. UNC investigators have developed assays to measure a) *antibody* to the key SARS-CoV2 *spike* protein, and b) levels of *neutralizing antibodies* which block infection. The program will increase the availability of titer-confirmed CCP to hospitalized patients in the UNC Health system. Further, will allow us to conduct an ethical but randomized control trial, in which all patients are treated with CCP, to answer critically important questions:

1) Are clinical outcomes better, worse or the same after high-titer CCP than CCP of standard titer?
2) Does the level of Spike antibody (a simple assay suitable for broad clinical laboratory use) predict neutralization titer (a difficult assay)? If so, CCP could be assessed for therapeutic use without a highly specialized research facility.

MILESTONES (300 word limit)
Description of what will be accomplished and what can be delivered by August 31, 2020, and by Dec. 31, 2020. The start date will be June 1, 2020.

August 31,2020 Milestones

CCP Use at UNC Hospitals: We will treat 50 hospitalized patients with antibody-titered CCP. At least half of these patients will have enrolled in our Standard versus High-Titer CCP trial (FDA IND 22282). For patients enrolled in the trial, we will have begun biobanking of a) blood and other body fluids for clinical use and b) paired mucosal fluids (nasal, respiratory, and intestinal) obtained both prior to and at timepoints after CCP infusion.

Convalescent donor recruitment and collections: We will have collected CCP from at least 40 donors (20 per month), with a measurement of the total antibody level and neutralizing antibody titers. Our donor recruitment team will have expanded outreach, donor transportation services, and storage capacity to increase collections from 20 to >30 donors per month.

Expansion to other UNC Health affiliates: We will have established a second collection center and procedures to deliver units to be given at different UNC Health hospitals.

December 31, 2020 Milestones

Convalescent donor recruitment and collections: We will have collected at least 360 units of CCP at UNC Hospital and at least another 180 units of CCP from a second collection center. At 2 units per patient, we will have treated 270 hospitalized patients within the UNC Health System and will have met sample size enrollment requirements for our trial.

Outcomes: We will have collected preliminary clinical outcome data to determine if CCP is effective and if titer matters. Bioassays will be completed on samples collected prior to November 1. We will have performed an initial analysis of whether CCP titer has an effect on SARS-CoV2 viral loads, recipient antibody levels, and blood and mucosal inflammatory responses. Processing and measurement of biomarkers that predict Covid-19 disease severity and CCP response will have been completed on a subset of participants.

BUDGET JUSTIFICATION (200 word limit)
Funds are limited. We encourage all teams to revisit their budget and determine if it can be reduced.

Total budget= $1,615,000

Personnel
$623,180

Support for Clinical and Research faculty, Clinical staff, Research Staff, Graduate Students, Research Fellow, and Regulatory and Data specialists

Travel
$7200

Donor and sample transportation costs: $7200

Supplies
$366,672

Includes clinical supplies and standard donor safety testing, and research supplies and reagents

Equipment
$147,400

Plasma harvest and banking equipment ($67,400) and automated liquid dispenser; ELISA Plate reader; -80C and -20C storage freezers ($80,000)
Clinical costs for 140 collections at UNC = $315,000
Contract costs for 40 collections at commercial center(s) = $120,000

Contracted Services
$130,000

Plasma collections at the blood center ($120,000) and sequencing costs ($10,000)

Tuition and fees
$12,000

For two Graduate Students (0.5 FTE each)

Patient Care Costs
$315,000

Clinical Costs for 140 collections

Other
$13,548

Service contracts for project equipment

Personnel Table

EHRA Salaries	$ 224,273.11
SHRA Salaries	$ 103,667.75
Grad Student	$ 25,000.00
Temps	$ 124,206.50
Fringe Pool	$ 133,065.16
Non-Personnel expenses	$ 1,004,787.48
TOTAL	$ 1,615,000.00